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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	22

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/658,537	Applicant(s) PATON ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *117-119* is/are allowed.

6)☒ Claim(s) *1,3,8,9,15,37,41,43,45-52,57,66,67,69,70,72-74,76,77,84,85,121 and 122* is/are rejected.

7)☒ Claim(s) *59 and 120* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1,3,8,9,15,37,41,43,45-52,57,59,66,67,69,70,72 74,76,77,84,85 and 117-122.

DETAILED ACTION

Non-Final Rejection

Claims 1, 3, 8, 9, 15, 37, 41, 43, 45-52, 57, 59, 66, 67, 69, 70, 72-74, 76, 77, 84, 85 and 117-122 are pending examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/28/03 has been entered.

Applicants' traversal, the amendment to claims 1, 3, 8, 9, 15, 37, 41, 43, 45-52, 57, 59, 66, 67, 69, 73, 74, 76, 77, 84, 85, 117, 118, and 119, the cancellation of claims 2, 4-7, 10-14, 16-36, 38-40, 42, 44, 53-56, 58, 60-65, 68, 71, 75, 78-83, and 86-116, the addition of claims 120-122 in paper no. 21 is acknowledged and considered.

Specification

The disclosure remains objected to because it contains embedded hyperlinks (e.g., See page 47, last line) and/or other form of browser-executable code. Applicant is required to delete all of the embedded hyperlink and/or other form of browser-executable code. Please check the entire specification for any other embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claim 45 is objected to because of the following informalities: The wording of claim 45 is grammatically incorrect. Suggest inserting the term -- a -- before the word "natural" on line 2 of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 8, 9, 15, 37, 41, 43, 45-52, 57, 66, 67, 69, 70, 72, 73, 74, 76, 77, 84, and 85 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3, 8, 9, 15, 37, 41, 43, 45-52, 57, 66, 67, 69, 70, 72, 73, 74, 76, 77, 84, and 85 as best understood, are readable on a genus of a recombinant gram negative enteric that displays on its surface a binding moiety that acts as a receptor mimic, the binding moiety being a receptor mimic for a toxin of a pathogenic microorganism or an adhesion of a pathogenic microorganism, wherein the binding moiety consists of an oligosaccharide which comprises a sugar residue that is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the bacterium, wherein the genus of the recombinant bacterium

is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of recombinant microorganism that displays on its surface a binding moiety that competes with a ligand for binding to a receptor for the ligand, wherein the binding moiety comprises an oligosaccharide which comprises a sugar residue that is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the microorganism. Furthermore, the as-filed specification contemplates that the acceptor moiety is endogenous to the microorganism and the glycosyltransferase is encoded by an exogenous nucleic acid. The disclosure further teaches that the acceptor moiety can consist of lipids or oligosaccharides on the outer surface of the microorganism (page 59). However, the as-filed specification and the art of record only provide sufficient description for sub-species (*E.Coli* and *S.typhimurium*) of a recombinant microorganism. The specification contemplates the production of Gm1, which is a mimicked by the LPS outer core of several Camplyobacter jejuni strains and using the sequence data the appropriate genes can be identified for assembly of the Gm1 mimic. One skilled in the art would consider the technology novel for describing a genus of the claimed recombinant bacterium. In addition, the genus of acceptor moiety of different gram-negative enteric bacterium varies depending on the species. The specification teaches that, "the outer region of the core of oligosaccharide comprises hexoses, which are linked to the inner core by a variety of highly

specific glycosyl transferases. Thus, the region varies in structure from species to species and even within a given bacterial strain" (page 42). Therefore, in view of the specification and the art of record, one skilled in the art would conclude E.coli and other species of gram negative enteric bacteria are physically and structurally different from each other and each bacterium comprises of numerous genes including genes that are involved in transferring receptors to the outside surface of the bacterium and the specification does not disclose a representative species of acceptor moieties. The as-filed specification fails to provide sufficient description of a genus of binding moieties that is considered an essential feature of the bacterium. This essential feature is required for one skilled in the art to practice the claimed invention because the binding moiety is used to compete with a ligand (e.g. receptor for a toxin) that binds to an endogenous receptor in an animal to reduce the level of that particular toxin in the animal. The art of record discloses linking a Shiga toxigenic receptor (Stx2) to a mutated LPS in an E.coli to produce a recombinant E.coli (Paton et al. Nature Medicine, Vol. 6, pp. 265-270, 2000). Furthermore, Paton teaches that, "many bacterial and viral pathogens exploit oligosaccharide moieties of glycoproteins or glycolipids on the surface of eukaryotic cells as receptors for toxins, adhesions, or other ligands".

It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of recombinant gram-negative enteric bacterium as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of recombinant gram

negative enteric bacterium that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a recombinant gram negative enteric bacterium. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. The claiming of a genus of recombinant gram-negative enteric bacterium that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). The skilled artisan cannot envision the detailed structure of a genus of a recombinant gram negative enteric bacterium contemplated by the claims that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 7/28/03 have been fully considered but they are not persuasive for the reasons set forth above.

The argument that, "claim 117 is directed to E.coli and dependent claims 118 and 119 recite specific oligosaccharides that act as receptor mimics (see page 16)," is moot because claims 117-119 are not rejected under the written description rejection.

The argument that, "applicants description of both E.coli and Salmonella enterica sv tymphimurium bacteria in the specification represents number of species that make up the claimed genus (see page 16)," is not found persuasive. The argument is not found persuasive because the as-filed specification fails to describe the genus of acceptor moiety of different gram-negative enteric bacterium varies depending on the species. The specification teaches that, "the outer region of the core of oligosaccharide comprises hexoses, which are linked to the inner core by a variety of highly specific glycosyl transferases. Thus, the region varies in structure from species to species and even within a given bacterial strain" (page 42). Therefore, in view of the specification and the art of record, one skilled in the art would conclude E.coli and other species of gram negative enteric bacteria are physically and structurally different from each other and each bacterium comprises of numerous genes including genes that are involved in transferring receptors to the outside surface of the bacterium and the specification does not disclose a representative species of acceptor moieties. The as-filed specification fails to provide sufficient description of a genus of binding moieties that is considered an essential feature of the bacterium. This essential feature is required for one skilled in the art to practice the claimed invention because the binding moiety is used to compete with a ligand (e.g. receptor for a toxin)

that binds to an endogenous receptor in an animal to reduce the level of that particular toxin in the animal.

The argument that, "it is submitted that a person in the present field of endeavour would clearly accept that the inventors have produced a receptor mimic in S.tymphimurium and also the present invention is applicable to other bacteria (see page 16)," is not found persuasive for reasons set forth above. Applicants provide no guidance to the art or factual evidence to support the assertion. See MPEP § 716.01(c).

The argument that, "the reference to enteric bacteria further limits the scope of the claimed beyond gram negative to those that are associated with the gastrointestinal tract (see page 16)," is not found persuasive for the reason set forth above.

Claims 1, 3, 8, 9, 15, 37, 41, 43, 45-52, 57, 59, 66, 67, 69, 70, 72, 73, 74, 76, 77, 84, 85, 121 and 122 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant *E.Coli* and *S.typhimurium*, does not reasonably provide enablement for a recombinant gram negative enteric bacterium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a recombinant gram negative enteric that displays on its surface a binding moiety that acts as a receptor mimic, the binding moiety being a receptor mimic for a toxin of a pathogenic microorganism or an adhesion of a pathogenic microorganism, wherein the binding moiety consists of an oligosaccharide which comprises a sugar residue that

is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the bacterium), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. used for producing a mimic of a receptor for a toxin on the cell surface of a recombinant microorganism using an acceptor moiety to transport the receptor to the outer surface.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is in the field of producing a recombinant gram-negative enteric bacterium comprising an exogenous nucleic acid encoding a glycosyltransferase that produces a receptor for a toxin and expressing the receptor on the surface of the bacterium. The field of the invention lies in genetically modifying a microorganism to express an exogenous nucleic acid encoding a glycosyltransferase that is operably linked to an acceptor moiety that is expressed on the outer surface of the microorganism.

A brief description of the examples (pages 41-66) provided by the as-filed specification follow: Example 1 is the construction of a harmless recombinant E.coli capable of incorporating the trisaccharide Galalpha[1-4]GalB[1-4]Glc into the outer core region of the its lipopolysaccharide, wherein the trisaccharide is capable of binding several types of Shiga toxin. Furthermore, the example encompasses testing the recombinant bacterium to protect mice from fatal infection with STEC. Example 2 examined the capacity of oral administration of killed recombinant E.coli to protect mice from otherwise fatal challenge of STEC. Example 3 is the construction of a recombinant E.coli expressing globotetraose on its surface and examined its

capacity to bind and neutralize STX2e in vitro. Example 4 teaches that C.difficle exotoxin A binds to several human glycolipids, all of which contain Galbeta[1-4]GlcNAc moiety and genes encoding transferase capable of assembling this epitope are also found in Neisseria IgT locus. Example 4 further contemplates the production of this epitope on recombinant bacterium and asserts that the capacity to bind and neutralize exotoxin A can be assessed using a standard protocol. The example further points out that in vitro studies indicate that even stronger binding occurs between exotoxin A and the trisaccharide Galalpha[1-3]Galbeta[1-4]GlcNAc-, even though it is not present in humans, see Karlsson, 1998, Mol. Microbiology. Therefore, a strain expressing this epitope can be constructed by incorporation a gene encoding a transferase capable of forming the necessary epitope and a database search for a source of such a transferase. Example 5 contemplates the production of Gm1, which is a mimicked by the LPS outer core of several Camplyobacter jejuni strains and using the sequence data the appropriate genes can be identified for assembly of the Gm1 mimic. Examples 6-8 contemplate extrapolating from the model systems discussed above to block bacterial adhesion. Example 9 is the production of detection method using the recombinant microorganism constructed or contemplated by the above examples.

In view of the breadth of the claims, the working examples, the guidance provided by the as-filed specification; and the art of record, the claimed invention provides sufficient guidance for one skilled in the art to make and/or use a recombinant *E.Coli* and *S.typhimurium* comprising an exogenous nucleic acid encoding a glycosyltransferase operably linked to a gene encoding an endogenous lipopolysaccharide that is expressed on the surface of the microorganism, wherein the expression of the exogenous nucleic acid results in a mimic of a receptor for a toxin of a

pathogenic microorganism. However, the claimed invention is not enabled for the full scope of the claimed invention because the as-filed specification fails to provide sufficient guidance for one skilled in the art to make and use a genus of recombinant gram-negative enteric bacterium for the following reasons:

First, with respect to the claimed invention comprising the making and/or using of a genus of recombinant gram-negative enteric bacterium, the disclosure only provides sufficient guidance for one skilled in the art to make and/or use the bacterium, *E.Coli* and *S.typhimurium*; because the as-filed specification fails to provide sufficient guidance for one skilled in the art to make and/or use an essential feature of the bacterium that is attaching a binding moiety (e.g. sugar residue, that is a mimic of a receptor on a pathogenic microorganism) to an acceptor moiety (e.g. lipopolysaccharide (LPS) that is transported to the exterior cell surface of the microorganism). This essential feature is required for one skilled in the art to practice the claimed invention because the binding moiety is used to compete with a ligand (e.g. receptor for a toxin) that binds to an endogenous receptor in an animal to reduce the level of that particular toxin in the animal. The art of record teaches linking a Shiga toxigenic receptor (Stx2) to a mutated LPS in an E.coli to produce a recombinant E.coli and using the recombinant microorganism to protect mice from challenge with an otherwise 100% fatal dose of Shige toxigenic E.coli (Paton et al. Nature Medicine, 2000). Furthermore, Paton teaches that, "many bacterial and viral pathogens exploit oligosaccharide moieties of glycoproteins or glycolipids on the surface of eukaryotic cells as receptors for toxins, adhesions, or other ligands. Construction of a given mimic requires the identification of the specific glycosyltransferase required for synthesis, and insertion of gene encoding these into a heterologous host producing appropriate

surface-expressed acceptor molecule" (Paton, pages 267-268). E.coli is a species of the genus, Gram-negative enteric bacteria, which have a LPS, which is an essential component of bacterial cell surface of this genus. The art of record is absent for using the surface-expressed LPS from E.coli as an accepted model for reasonably extrapolating to a genus of surface-expressed acceptor molecule in a genus of gram-negative bacteria. Therefore, in view of the unpredictability of the identifying a representative number of gram negative enteric bacteria with a surface-expressed acceptor molecule that can be used for attaching an binding moiety to and expressing the cell's surface, it would take one skilled in the art an undue amount of experimentation to reasonably correlate from making and/or using a recombinant E.coli to practicing the full breadth of the claimed invention.

Furthermore, there are concerns provided by the state of the art for expressing an exogenous nucleic acid encoding a glycosyltransferase operably linked to an appropriate surface-expressed acceptor molecule in a representative number of microorganisms. At the time the invention was filed, the as-filed specification provides sufficient guidance for expressing an exogenous nucleic acid in E.coli and one skilled in the art would have been enabled to make and/or use species of gram-negative enteric bacteria to express an exogenous nucleic acid encoding a glycosyltransferase in a culture and isolating exogenous nucleic acid from the culture. However, at the time application was filed and in view of the breadth of the claimed invention, the as-filed specification fails to provide sufficient guidance for one skilled in the art to make and/or use a representative number of species for one skilled in the art to practice the full scope of the claimed invention because the disclosure does not provide sufficient guidance for what bacterium are/are not considered enabled for one skilled in the art to make and/or use, which

would require an undue amount of experimentation for one skilled in the art to reasonably extrapolate from the working examples using E.coli in the as-filed specification to a genus of microorganisms. For example, the art of record teaches that replication of plasmid DNA in gram-negative bacteria is dependent on three stages; initiation, elongation, and termination. The first stage, initiation depends on plasmid-encoded properties such as the replication origin (oriC) and in most cases, the replication initiation protein (Rep protein). Most plasmid studies exhibit a narrow host range limited to E.coli and related bacteria (Kues et al., Replication of plasmids in gram-negative bacteria, Micriobiol Rev., Vol. 53, 1989, (abstract) Medline [online], Bethesda, MD USA: United States National Library of Medicine [retrieved on 6/26/02], Medline accession number 2687680; Yazawa et al., Breast Cancer Research and Treatment, Vol. 66, pp. 165-170, 2001 and Argnani et al., Microbiology, Vol. 142, pp. 109-114). The art of record also teaches that several species of oriC have been isolated (Moriya et al., Plasmid, Vol. 41, pp. 17-29, 1999). Moriya teaches that:

> Studies in E.coli have taken the lead in research of initiation mechanism of the bacterial chromosome replication and have provided considerable insight into this key regulation mechanism which is thought to be basically common in eubacteria. However, the picture is far from clear. In Bacillus Subtilis, our studies suggest that the mechanism that determines the time of initiation of chromosome replication is different from E.coli (page 17). Further analysis of initiation of replication using new technology will help elucidate the key mechanisms controlling bacterial cell cycle (page 26).

In view of the art of record and the lack of guidance provided by the as-filed specification for the making and/or using the genus of gram-negative enteric bacterium), the as-filed specification

only provides sufficient guidance for one skilled in the art to make and/or use E.coli in the claimed invention because of the reasons set forth above. See Enzo 188 F.3d at 1374, 52 USPQ2d at 1138. Thus, it is not apparent as to how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of bacteria (*E.Coli* and *S.typhimurium*) to the full scope of the claimed invention that would display a binding moiety that competes with a ligand for binding a receptor for the ligand.

Furthermore, with respect to the pharmaceutical composition comprising a recombinant gram negative enteric bacterium set forth in claims 66, 67, 69, 70, 72, 73, 74, 76, 77, 84, 85, 121 and 122, the only therapeutic usage taught in the specification is for administering a recombinant bacterium to a mammal to reduce adherence of a pathogen or a toxin produced by the pathogen in the mucosal surface of the mammal. The as-filed specification fails to provide sufficient guidance for how controlled experiments using mice reasonably correlate to reducing adherence of a pathogen or a toxin produced by the pathogen in the mucosal surface of the mammal because the state of the art teaches that commencement of therapy immediately after challenge was 100% protective, but in a mammal setting such early intervention will be possible only for patients with confirmed cases, who have not yet, or have only just, become infected with a pathogenic microorganism (Paton et al., Infection and Immunity, Vol. 69, pp. 1389-1393, 2001). The specification does not teach how to identify what mammals have or have not or have only just become infected with a pathogenic microorganism. Thus, it is not apparent to one skilled in the art how to use the pharmaceutical composition in any method sought forth in the specification because of the unpredictability of determining when a mammal has, does not yet have, or have only just become infected with a microorganism and if at later time points in the

infection the recombinant microorganism can reduce the amount of toxin in the mammal. See Enzo 188 F.3d at 1374, 52 USPQ2d at 1138. Therefore, it would take an undue amount of experimentation for one skilled in the art to reasonably extrapolate from controlled experiments to using any pharmaceutical composition set forth in the claims for reducing adherence of a pathogen or a toxin produced by the pathogen in the mucosal surface of the mammal.

Thus, in view of the In re Wands' Factors, the disclosure is only enabled for a recombinant bacterium comprising an exogenous nucleic acid encoding a glycosyltransferase that produces a specific sugar moiety, which is a mimic of a sugar moiety from a specific bacteriological toxin, when expressed on the cell surface attached to a surface-expressed acceptor molecule of the recombinant gram negative enteric bacterium, wherein the recombinant bacterium is *E.Coli* or *S.typhimurium* and is not enabled for the full scope of the claimed invention because in view of the undue quantity of experimentation necessary to determine the parameters listed above for the starting material, the lack of direction or sufficient guidance provided by the as-filed specification for the production of a representative number of recombinant gram-negative enteric bacterium to practice the claimed invention. Furthermore, the lack of working examples for the demonstration or the reasonable correlation to the production of a genus of recombinant bacterium, in particular when the expression of a binding moiety attached to an acceptor moiety can compete with a toxin, the unpredictable state of the art with respect to the expressing an oligosaccharide attached to a LPS that is expressed on the cell's exterior surface, and the breadth of the claims drawn to any recombinant gram-negative bacterium, it would require an undue amount of experimentation for one skilled in the art to make and/or use the full scope of the claimed invention.

Applicant's arguments filed 7/28/03 have been fully considered but they are not persuasive for reasons set forth above. The majority of the arguments for the 112 first paragraph enablement rejection are the same arguments provided by the applicant under the 112 first paragraph written description rejection. The arguments are not found persuasive for the same reasons as set forth under 112 first paragraph written description. Furthermore, in view of the In Re Wands Factors, the specification fails to provide sufficient guidance and/or factual evidence for one skilled in the art to practice the full scope of the claimed invention.

In addition, applicant's argument that, "even if some bacterial species are unable to be transformed with a plasmid, claims reading on inoperative embodiment are enabled if the skilled artisan understands how to avoid inoperative embodiments (see page 18)." The argument is not found persuasive. On this record, it is apparent that the as-filed specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using any gram negative enteric bacterium in the claimed invention, for those skilled in the art to experiment with different gram negative enteric bacterium to make and use the genus of recombinant bacterium as intended by the as-filed specification at the time the invention was made. See Enzo 188 F.3d at 1374, 52 USPQ2d at 1138. See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what protocols are required for making and using different gram-negative enteric bacterium other than the sub-species E.coli and

S.typhimurium, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the scope listed above to the full breadth of claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 57 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 recites the limitation "the acceptor molecule". There is insufficient antecedent basis for this limitation in the claim.

Conclusion

Claims 117-119 are in condition for allowance because the claims are free of the prior art of record.

Claims 59 and 120 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER